



Atty. Dkt. No. 053466-0414
Appl. No. 10/574,860

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Shigeto KAWAI et al.
Title: THERAPEUTIC AGENTS FOR SOLID TUMORS
Appl. No.: 10/574,860
Filing Date: 04/06/2006
Examiner: Anne Gussow
Art Unit: 1643

DEPOSIT STATEMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Yasuo Koishihara, an inventor of the captioned application, declare:

1. A deposit of an anti-HM1.24 antibody-producing hybridoma was made at the following International Depository Authority, whose current address is:

Patent Microorganism Depository of the
National Institute of Industrial Science and Technology
Chuo Dai 6,
1-1, Higashi 1-chome
Tsukuba city, Ibaraki
Japan

under accession number FERM BP-5233 (deposit date: April 27, 1985) and accepted under the provisions of the Budapest Treaty for patent purposes.

2. All restrictions on the availability to the public of the culture deposited will be irrevocably removed upon the granting of a patent from the above-identified application;

3. The deposit will be replaced if viable samples cannot be dispensed by the depository; and,

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that

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these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom; Further declarant sayeth not.

Respectfully submitted,

Date July 9th, 2009

By Yasuo Koishihara

Yasuo Koishihara



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DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. YASUO KOISHIHARA

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Yasuo Koishihara, hereby declare and say that

I am a scientist employed by Chugai Pharmaceutical Co., Ltd. since 1984. I am presently employed as Group Manager of Assessment Coordination Group, Business Development Department. A copy of my CV is attached.

I established a screening method using EGF receptor binding assay for anticancer drugs in 1984.

I purified natural erythropoietin from the urine of anemia patients for the development of recombinant erythropoietin at Kumamoto University in 1985-87.

I was in charge of an IL-6 blocker's program in which we collaborated with Osaka University and then therapeutic monoclonal antibodies since 1987. First antibody program was development of humanized IL-6 receptor antibody for treatment of Multiple Myeloma and Rheumatoid Arthritis. Second program was development of humanized BST-2/HM1.24

(CD317) antibody in which collaborated with Tokushima University for treatment of Multiple Myeloma and other tumors since 1994.

The experiments of our BST-2/HM1.24 research were conducted by me or under my supervision and control. I am a co-inventor of the subject matter of the above-identified U.S. Patent application. I am familiar with the specification and pending claims, and with the prosecution history of the application.

Other than my regular salary, I have not been provided additional compensation for preparing this declaration.

I am able to read and understand the English language, when it is written;

I have reviewed the application and the examiner's anticipation rejection of claims 15-19, 21 and 22 of this application relating to therapeutic agents for solid tumors. Specifically, the examiner maintains that Morin *et al.* (US PG PUB 2003/0211498, "Morin") anticipates the claimed invention because "Morin specifically discusses these antibodies for treatment of ovarian cancer and since the BST-2 protein is identical to the instant SEQ ID No. 2 (see sequence alignment) the claims are anticipated by Morin." (Office Action dated January 16, 2009, page 7).

Morin simply places anti-BST-2 antibody in a long list of possible antibodies that could be used to treat ovarian cancer. Nowhere in the specification does Morin teach how to use or generate specific anti-HM1.24 antibodies to treat a disease. Additionally, Morin does not provide experimental proof that ovarian cancer can be treated by an anti-BST-2 antibody. In fact, no antibodies were prepared in the Morin reference. Specifically, Morin does not disclose the use of anti-HM1.24 antibodies. Thus, from the Morin specification one of skill in the art would not know how to prepare antibodies to treat ovarian cancer.

Additionally, the Morin reference does not disclose the relationship between expression of BST-2 antigen protein and the disease state. The Morin reference only shows that mRNA levels are increased in ovarian tumor cells, but does not show that protein levels are increased. Antibodies used to treat cancers are most effective if differentially expressed in cancer cells at the protein level. Morin does not teach the correlation between mRNA BST-2 levels and protein expression levels of BST-2. This is important because post-transcriptional regulation could play a key role in protein regulation. Specifically, in cancer cells increases in

mRNA levels do not always correlate to increases in protein expression levels. Thus, from the Morin reference, one of ordinary skill in the art would not necessarily focus on generating BST-2 antibodies to treat cancer.

I have reviewed K.M. Roppen *et al.*, *J. Clin Pathol* (2001), 54: 533-538, and the authors show that post-transcriptional regulation can modify the availability of functional AP-2 γ protein. Specifically, the authors state "Together with reduced AP-2 γ expression in high grade carcinomas, this might contribute to tumor progression. The discrepancy between mRNA and protein expression suggests that posttranscriptional regulatory mechanism might modify the availability of functional AP-2 γ protein in colorectal carcinoma."

Additionally, I have reviewed Fujimoto *et al.*, *Jpn. J. Electroph.* (1998) 40:313 25-28. In this reference, the authors argue that post-transcriptional regulation plays a key role in regulating protein levels in tumors. Specifically, the abstract states "A discrepancy between results of nm 23-H1 protein level by Western blot and mRNA level by Northern blot was observed in HCCs," and that "these data suggest that the expression of nm 23-H1 was mainly regulated at a post-transcriptional level." Taken together, the Roppen and Fujimoto references support the proposition that protein levels are not always correlated with mRNA levels in tumors.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Date

July 9th, 2009

Yasuo Koishihara
Dr. Yasuo Koishihara

CV of Yasuo Katsuhara

1984.04.01	Research Laboratory 4, New Drug Research Laboratory
1985.02.11	Research Dept. III, New Drug Research Laboratory
1985.04.01 - 1987.01.31	Researcher, Internal Medicine II, Medical School, Kumamoto University
1987.02.11	Research Dept. III, Exploratory Research Laboratory
1990.05.11	Research Dept. II, Exploratory Research Laboratory
1992.02.11	Researcher, Exploratory Research Laboratory I
1993.02.11	Assistant Manager, Laboratory of Cancer & Hematological Disease
1995.01.11	Research Scientist, Pharmaceutical Research Laboratory
1997.02.01	Senior Scientist, Pharmaceutical Research Laboratory
1997.10.01	Senior Scientist, Pharmaceutical Research Laboratory II
1998.10.01	Manager, Pharmaceutical Development Coordination Dept.
2000.10.01	Project Leader (AHM), Manager, International Development Coordination Dept.
2002.10.01	Specialist, Project Management Group, Project Management Dept.
2003.10.01	Specialist, Project Management Group, Development Planning Dept.
2005.07.01	Specialist, Project Management (PoC) Dept., Strategic Marketing Unit
2006.09.01	Leader, Assessment Coordination Group, Business Development Dept., Strategic Marketing Unit
2008.03.27	Leader, Assessment Coordination Group, Business Development Dept., Lifecycle Management & Marketing Unit
2008.10.01	Group Manager, Assessment Coordination Group, Business Development Dept., Lifecycle Management & Marketing Unit